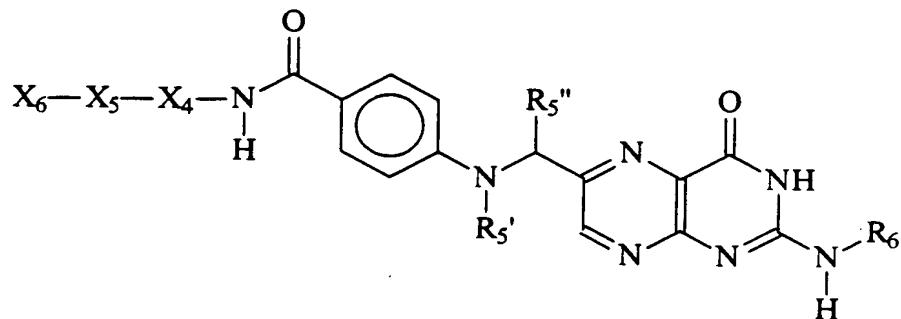


What is claimed is:

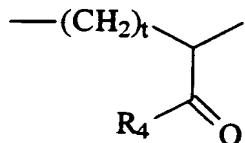
1. A compound of the formula:



wherein:

$\text{X}_4$  is  $-\text{CH}(\text{X}_4)$  or a group of formula:

5



$\text{X}_4$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

5  $\text{X}_5$  is  $-\text{N}(\text{X}_5)\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{NH}-$ ,  $-\text{NHC}(\text{O})-$ ,  $-\text{OC}(\text{O})\text{NH}-$ ,

10  $-\text{C}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{O})\text{NH}-$ ,  $-\text{OC}(\text{S})\text{NH}-$ ,  $-\text{C}(\text{O})\text{O}-$ ,  
 $-\text{C}(\text{O})(\text{CH}_2)_n-$  or a bond;

$n$  is an integer from 1 to 50;

each  $\text{X}_6$  and  $\text{X}'_6$  is, independently, hydrogen or a hydrocarbyl group selected from  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_2\text{-C}_{10}$  alkenyl,  
15  $\text{C}_2\text{-C}_{20}$  alkynyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_6\text{-C}_{14}$  aralkyl,  $\text{C}_3\text{-C}_{14}$  cycloalkyl,  
 $\text{C}_5\text{-C}_{14}$  fused cycloalkyl,  $\text{C}_4\text{-C}_{14}$  heterocycle,  $\text{C}_4\text{-C}_{14}$  heterocyclalkyl,  $\text{C}_4\text{-C}_{14}$  heteroaryl and  $\text{C}_4\text{-C}_{14}$  heteroarylalkyl;  
wherein said hydrocarbyl group is substituted with at least  
two hydroxyl groups, and is optionally substituted with oxo,  
20 acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino,  
amido, azido, aryl, heteroaryl, carboxylic acid, cyano,  
guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,

alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that  $X_6$  is not hydrogen;

5         $R_4$  is a hydroxyl group or a protected hydroxyl group;

$R_5$  is hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl or an amino-protecting group

$R_5$  is hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl,  $C_6-C_{14}$  aralkyl,  $C_3-C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

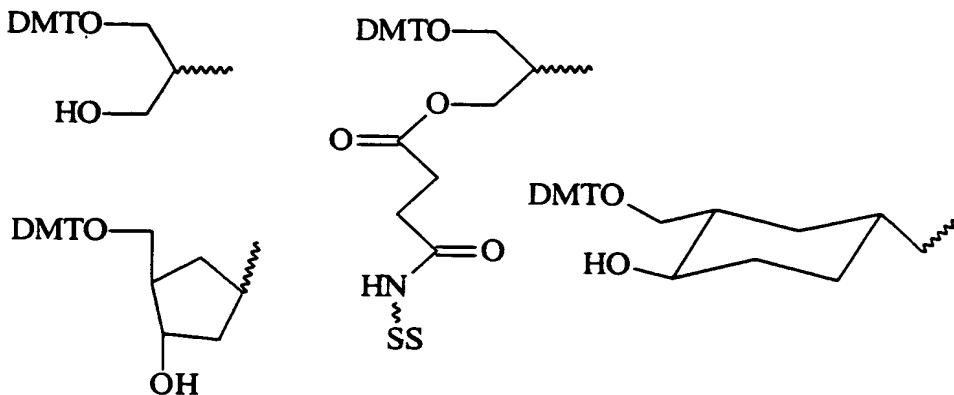
10       $R_6$  is hydrogen or an amino protecting group; and  
          t is 1 or 2.

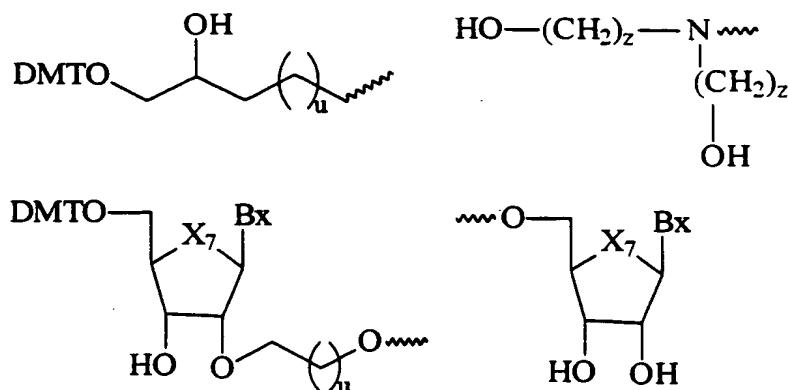
2.       The compound of claim 1 wherein said amino acid is  
          amino caproic acid.

3.       The compound of claim 1 connected to an  
15 oligonucleotide by a disulfide group.

4.       The compound of claim 1 wherein said  $X_4$  is the side  
          chain of glutamic acid.

5.       The compound of claim 1 wherein said  $X_6$  has one of  
          the formulas:





wherein:

SS is a solid support;

X<sub>7</sub> is O or CH<sub>2</sub>;

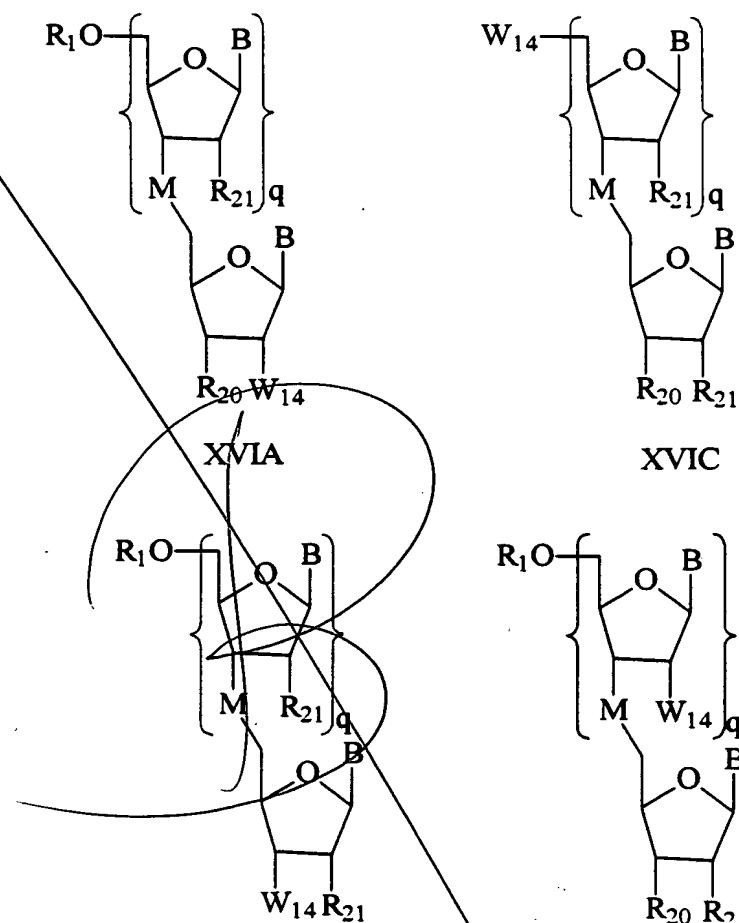
Bx is a nucleobase, C<sub>4</sub>-C<sub>14</sub> heterocyclyl or hydrogen;

5 z is an integer from 1 to 50; and

u is an integer from 2 to 5.

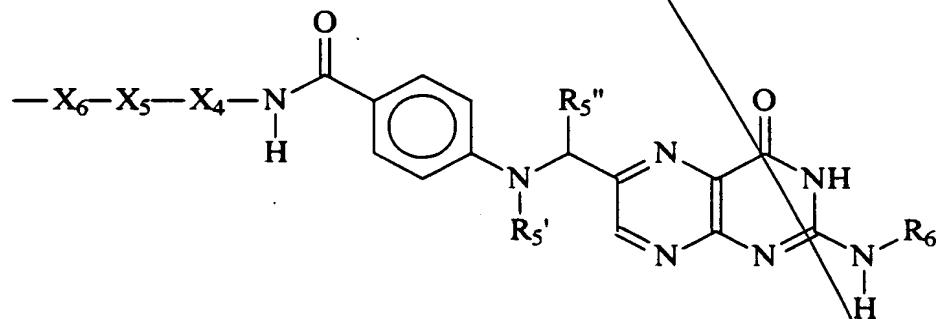
6. The compound of claim 1 wherein said X<sub>6</sub> is attached to a solid support.

7. A compound having formula XVIA, XVIB, XVIC or XVID:



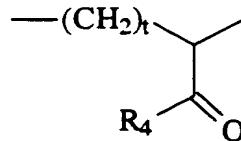
wherein:

W<sub>14</sub> has the formula:



wherein:

X<sub>4</sub> is -CH(X<sub>4'</sub>) or a group of formula:



$X_4$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

5 t is 1 or 2;

$X_5$  is  $-N(X_6)C(O)-$ ,  $-C(O)NH-$ ,  $-NHC(O)-$ ,  $-OC(O)NH-$ ,  
 $-C(S)NH-$ ,  $-SC(S)NH-$ ,  $-SC(O)NH-$ ,  $-OC(S)NH-$ ,  $-C(O)O-$ ,  
 $-C(O)(CH_2)_n-$  or a bond;

n is an integer from 1 to 50;

10 each  $X_6$  and  $X_6'$  is, independently, a bond, hydrogen or a hydrocarbyl group selected from  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl,  $C_6-C_{14}$  aralkyl,  $C_3-C_{14}$  cycloalkyl,  $C_5-C_{14}$  fused cycloalkyl,  $C_4-C_{14}$  heterocycle,  $C_4-C_{14}$  heterocyclalkyl,  $C_4-C_{14}$  heteroaryl and  $C_4-C_{14}$  heteroarylalkyl;  
15 wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,  
20 alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that  $X_6$  is not hydrogen and  $X_6'$  is not a bond;

$R_1$  is hydrogen or a hydroxyl protecting group;

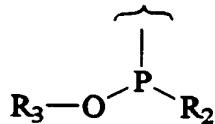
$R_4$  is a hydroxyl group or a protected hydroxyl group;

25 each  $R_5$  and  $R_{40}$  is, independently, hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl or an amino-protecting group

$R_5$  is hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl,  $C_6-C_{14}$  aralkyl,  $C_3-C_{14}$  cycloalkyl, formyl,  
30 aminoalkyl or hydroxymethyl;

$R_6$  is hydrogen or an amino protecting group;

$R_{20}$  is hydrogen or a group of formula:



$R_2$  is  $-N(R_7)_2$ , or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and  
5 having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

$R_1$  is straight or branched chain alkyl having from 1 to 10 carbons;

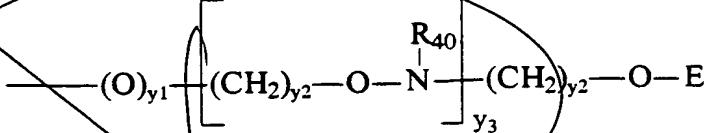
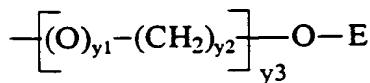
10  $R_{21}$  is hydrogen, hydroxyl, fluoro or a group of formula  $Z-R_{22}-(R_{23})_v$ ;

$Z$  is O, S, NH or  $N-R_{22}-(R_{23})_v$ ;

$R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

15  $R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, 20 disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

25 or  $R_{21}$  has one of the formulas:



wherein:

$y_1$  is 0 or 1;

each  $y_2$  is, independently, 0 to 10;

5  $y_3$  is 1 to 10;

$E$  is  $N(R_{41})(R_{42})$  or  $N=C(R_{41})(R_{42})$ ;

each  $R_{41}$  and each  $R_{42}$  is independently H,  $C_1-C_{10}$  alkyl, a nitrogen protecting group, or  $R_{41}$  and  $R_{42}$  taken together form a nitrogen protecting group; or  $R_{41}$  and  $R_{42}$  taken together with 10 the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

B is a nucleobase;

M is an optionally protected internucleoside linkage;

15 q is from zero to about 50; and  
v is from zero to about 10.

101

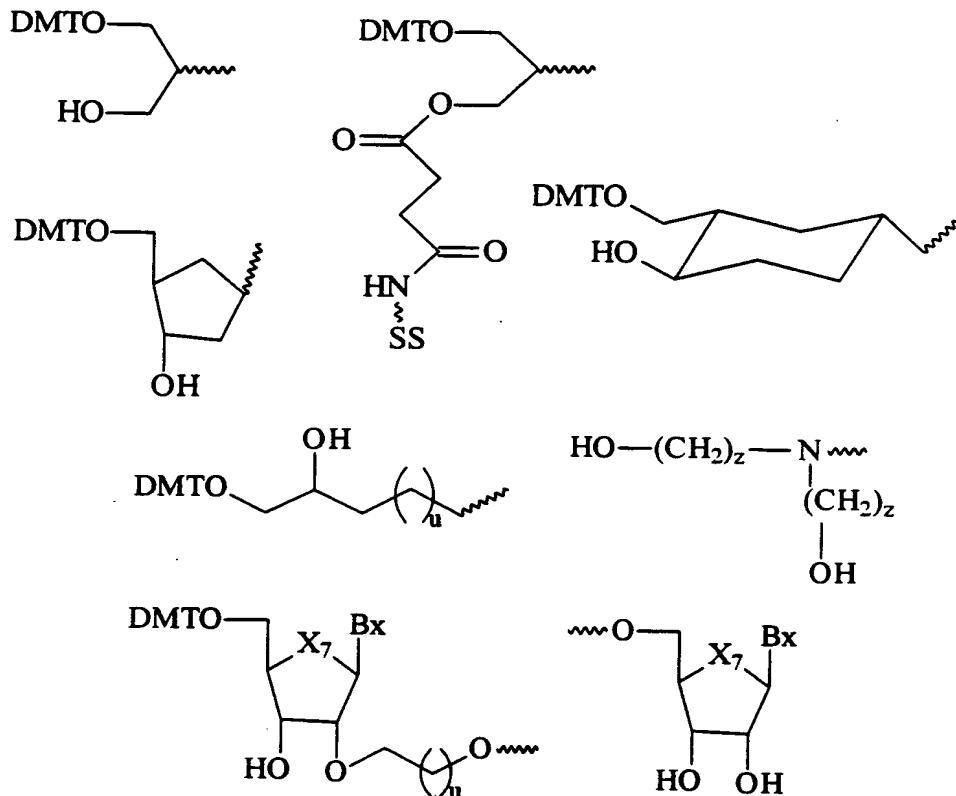
B 8. The compound of claim A wherein said amino acid is  
amino caproic acid.

101

B 9. The compound of claim A wherein said  $X_4$  is the side  
20 chain of glutamic acid.

101

B 10. The compound of claim A wherein said  $X_6$  has one of  
the formulas:

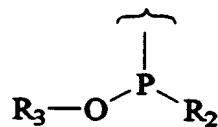


wherein

- SS is a solid support;  
 5 X<sub>7</sub> is O or CH<sub>2</sub>;  
 Bx is a nucleobase, C<sub>4</sub>-C<sub>14</sub> heterocyclyl or hydrogen;  
 z is an integer from 1 to 50; and  
 u is an integer from 2 to 5.

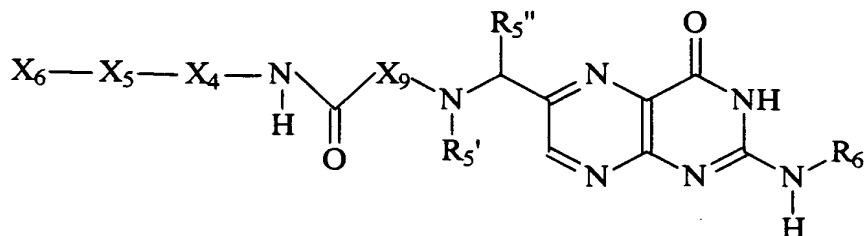
B 11. The compound of claim <sup>10/</sup><sub>A</sub> wherein said R<sub>1</sub> is  
 10 dimethoxytrityl.

B 12. The compound of claim <sup>10/</sup><sub>A</sub> wherein said R<sub>20</sub> is a group  
 of formula:



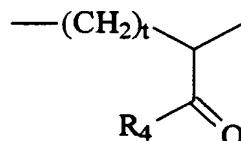
wherein R<sub>2</sub> is diisopropylamino and R<sub>3</sub> is β-cyanoethyl.

13. A compound of the formula:



wherein:

X<sub>4</sub> is -CH(X<sub>4'</sub>) or a group of formula:



X<sub>4'</sub> is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

- X<sub>5</sub> is -N(X<sub>6'</sub>)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-,  
 10 -C(S)NH-, -SC(S)NH-, -SC(O)NH-, -OC(S)NH-, -C(O)O-,  
 -C(O)(CH<sub>2</sub>)<sub>n</sub>- or a bond;  
 n is an integer from 1 to 50;  
 each X<sub>6</sub>, X<sub>6'</sub> and X<sub>9</sub> is, independently, a bond, hydrogen or  
 a hydrocarbyl group selected from C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl,  
 15 C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>6</sub>-C<sub>14</sub> aralkyl, C<sub>3</sub>-C<sub>14</sub> cycloalkyl,  
 C<sub>5</sub>-C<sub>14</sub> fused cycloalkyl, C<sub>4</sub>-C<sub>14</sub> heterocycle, C<sub>4</sub>-C<sub>14</sub>  
 heterocyclalkyl, C<sub>4</sub>-C<sub>14</sub> heteroaryl and C<sub>4</sub>-C<sub>14</sub> heteroarylalkyl;  
 wherein said hydrocarbyl group is substituted with at least  
 two hydroxyl groups, and is optionally substituted with oxo,  
 20 acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino,  
 amido, azido, aryl, heteroaryl, carboxylic acid, cyano,  
 guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,  
 alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that each of  $X_6$  and  $X_6'$  is not a bond and  $X_6$  is not hydrogen;

$R_4$  is a hydroxyl group or a protected hydroxyl group;

$R_5$  is hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl or an amino-protecting group

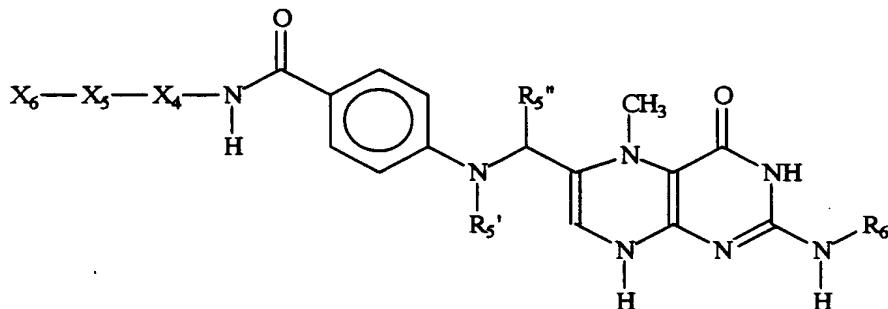
$R_5'$  is hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl,  $C_6-C_{14}$  aralkyl,  $C_3-C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

$R_6$  is hydrogen or an amino protecting group; and  
10  $t$  is 1 or 2.

14. The compound of claim 13 wherein said amino acid is aminocaproic acid

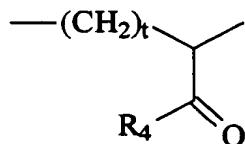
15. The compound of claim 13 connected to an oligonucleotide by a disulfide group.

15 16. A compound of the formula:



wherein:

$X_4$  is  $-CH(X_4)$  or a group of formula:



$X_4$  is the side chain of a naturally-occurring or non-  
20 naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

X<sub>5</sub> is -N(X<sub>6</sub>)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -C(S)NH-, -SC(S)NH-, -SC(O)NH-, -OC(S)NH-, -C(O)O-, -C(O)(CH<sub>2</sub>)<sub>n</sub>- or a bond;

n is an integer from 1 to 50;

- 5 each X<sub>6</sub> and X<sub>6'</sub> is, independently, hydrogen or a hydrocarbyl group selected from C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>6</sub>-C<sub>14</sub> aralkyl, C<sub>3</sub>-C<sub>14</sub> cycloalkyl, C<sub>5</sub>-C<sub>14</sub> fused cycloalkyl, C<sub>4</sub>-C<sub>14</sub> heterocycle, C<sub>4</sub>-C<sub>14</sub> heterocyclylalkyl, C<sub>4</sub>-C<sub>14</sub> heteroaryl and C<sub>4</sub>-C<sub>14</sub> heteroarylalkyl;
- 10 wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and optionally substituted with oxo, acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,
- 15 alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X<sub>6</sub> is not hydrogen;

R<sub>4</sub> is a hydroxyl group or a protected hydroxyl group;

R<sub>5</sub>' is hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub>

- 20 alkynyl, C<sub>6</sub>-C<sub>14</sub> aryl or an amino-protecting group

R<sub>5</sub>.. is hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>6</sub>-C<sub>14</sub> aralkyl, C<sub>3</sub>-C<sub>14</sub> cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

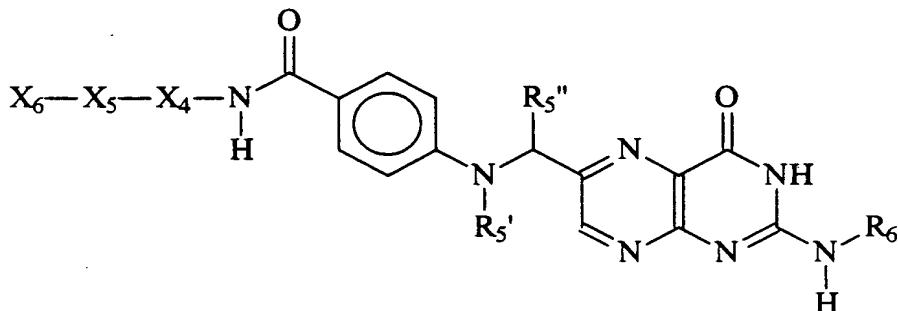
R<sub>6</sub> is hydrogen or an amino protecting group; and

- 25 t is 1 or 2.

17. The compound of claim 16 wherein said amino acid is aminocaproic acid.

18. The compound of claim 16 connected to an oligonucleotide by a disulfide group.

- 30 19. A method of preparing compounds of formula XVII:

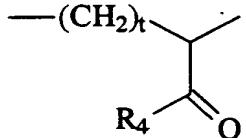


XVII

wherein:

 $\text{X}_4$  is  $-\text{CH}(\text{X}_4')$  or a group of formula:

5



$\text{X}_4'$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

- $\text{X}_5$  is  $-\text{N}(\text{X}_6')\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{NH}-$ ,  $-\text{NHC}(\text{O})-$ ,  $-\text{OC}(\text{O})\text{NH}-$ ,  
 10  $-\text{C}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{O})\text{NH}-$ ,  $-\text{OC}(\text{S})\text{NH}-$ ,  $-\text{C}(\text{O})\text{O}-$ ,  
 $-\text{C}(\text{O})(\text{CH}_2)_n-$  or a bond;  
 n is an integer from 1 to 50;  
 each  $\text{X}_6'$  and  $\text{X}_6$  is, independently, hydrogen or a hydrocarbyl group selected from  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_2\text{-C}_{10}$  alkenyl,  
 15  $\text{C}_2\text{-C}_{20}$  alkynyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_6\text{-C}_{14}$  aralkyl,  $\text{C}_3\text{-C}_{14}$  cycloalkyl,  $\text{C}_5\text{-C}_{14}$  fused cycloalkyl,  $\text{C}_4\text{-C}_{14}$  heterocycle,  $\text{C}_4\text{-C}_{14}$  heterocyclalkyl,  $\text{C}_4\text{-C}_{14}$  heteroaryl and  $\text{C}_4\text{-C}_{14}$  heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that  $X_6$  is not hydrogen;

$R_4$  is a hydroxyl group or a protected hydroxyl group;

$R_5$  is hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$

5 alkynyl,  $C_6-C_{14}$  aryl or an amino-protecting group

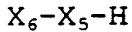
$R_5$  is hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl,  $C_6-C_{14}$  aralkyl,  $C_3-C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

$R_6$  is hydrogen or an amino protecting group; and

10  $t$  is 1 or 2;

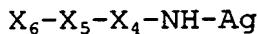
comprising the steps of:

(a) providing a hydroxy compound of formula:



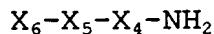
(b) protecting said hydroxyl groups of  $X_6$  with protecting groups to form a protected hydroxy compound;

15 (c) reacting said protected hydroxy compound with an amino-protected amino acid to form a covalently linked hydroxy compound of formula:



20 wherein Ag is an amino protecting group;

(d) cleaving the amino-protecting group of said covalently linked hydroxy compound to form a hydroxy compound bearing a deprotected amino group and having formula:



25 (e) reacting said amino group with a folate moiety; and

(f) cleaving the protecting groups on said hydroxyl groups of step (b) to form a compound of formula XVII.

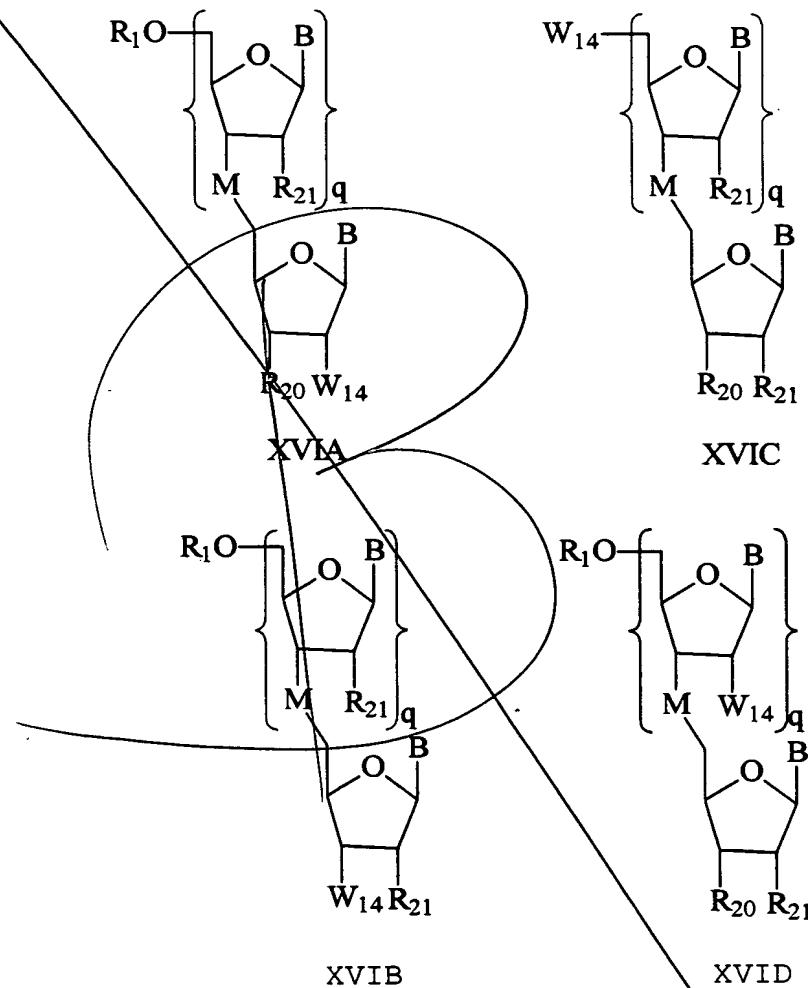
20. The method of claim 19 further comprising the steps of:

30 (g) protecting one of said hydroxyl groups of  $X_6$  with a dimethoxytrityl group; and

(h) phosphorylating the other of said hydroxyl groups of

X<sub>6</sub>.

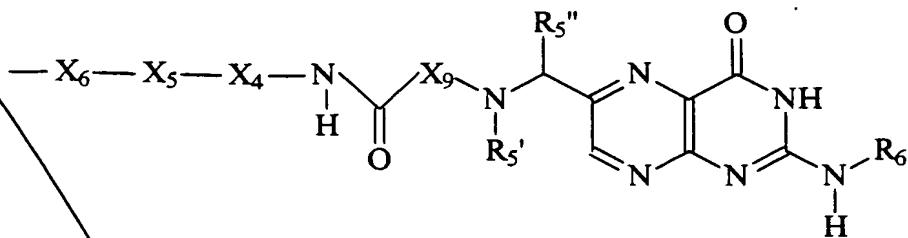
21. A compound having formula XVIA, XVIB, XVIC or XVID:



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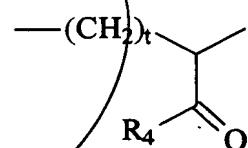
wherein:

W<sub>14</sub> has the formula:



wherein:

$X_4$  is  $-\text{CH}(X_{4'})$  or a group of formula:



$X_{4'}$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

5  $t$  is 1 or 2;

$X_5$  is  $-\text{N}(X_6) \text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{NH}-$ ,  $-\text{NHC}(\text{O})-$ ,  $-\text{OC}(\text{O})\text{NH}-$ ,

- $\text{C}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{O})\text{NH}-$ ,  $-\text{OC}(\text{S})\text{NH}-$ ,  $-\text{C}(\text{O})\text{O}-$ ,

10  $-\text{C}(\text{O})(\text{CH}_2)_n-$  or a bond;

$n$  is an integer from 1 to 50;

each  $X_6$ ,  $X_6'$  and  $X_9$  is, independently, a bond, hydrogen or a hydrocarbyl group selected from  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_2\text{-C}_{20}$  alkynyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_6\text{-C}_{14}$  aralkyl,  $\text{C}_3\text{-C}_{14}$  cycloalkyl,

15  $\text{C}_5\text{-C}_{14}$  fused cycloalkyl,  $\text{C}_4\text{-C}_{14}$  heterocycle,  $\text{C}_4\text{-C}_{14}$  heterocyclalkyl,  $\text{C}_4\text{-C}_{14}$  heteroaryl and  $\text{C}_4\text{-C}_{14}$  heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino,

20 amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that each  $X_6$  and  $X_9$  is not hydrogen and  $X_6$  is not a bond;

$R_1$  is hydrogen or a hydroxyl protecting group;

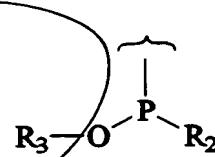
$R_4$  is a hydroxyl group or a protected hydroxyl group;

5 each  $R_5$  and  $R_{40}$  is, independently, hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl or an amino-protecting group

10  $R_5$  is hydrogen,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_6-C_{14}$  aryl,  $C_6-C_{14}$  aralkyl,  $C_3-C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

$R_6$  is hydrogen or an amino protecting group;

$R_{20}$  is hydrogen or a group of formula:



15  $R_2$  is  $-\text{N}(\text{R}_7)_2$ , or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

20  $R_7$  is straight or branched chain alkyl having from 1 to 10 carbons;

20  $R_3$  is a phosphorus protecting group;

$R_{21}$  is hydrogen, hydroxyl, fluoro or a group of formula  $Z-\text{R}_{22}-(\text{R}_{23})_v$ ;

$Z$  is O, S, NH or  $\text{N}-\text{R}_{22}-(\text{R}_{23})_v$ ;

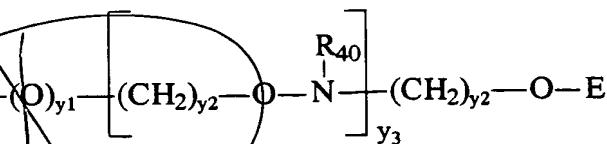
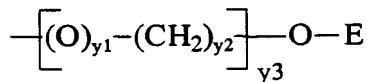
$R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

25  $R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino,

30 hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide,

~~polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;~~

5 or  $R_{21}$  has one of the formulas:



wherein:

y<sub>1</sub> is 0 or 1;

each y<sub>2</sub> is, independently, 0 to 10;

10 y<sub>3</sub> is 1 to 10;

E is N( $R_{41}$ ) ( $R_{42}$ ) or N=C( $R_{41}$ ) ( $R_{42}$ );

each  $R_{41}$  and each  $R_{42}$  is independently H, C<sub>1</sub>-C<sub>10</sub> alkyl, a nitrogen protecting group, or  $R_{41}$  and  $R_{42}$  taken together form a nitrogen protecting group; or  $R_{41}$  and  $R_{42}$  taken together with

15 the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

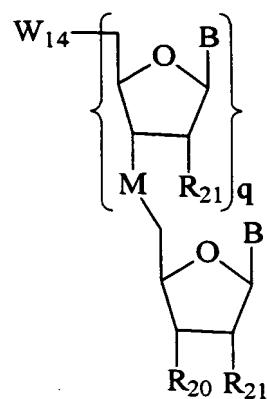
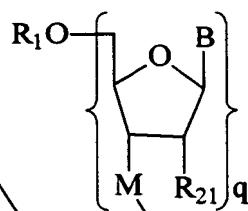
B is a nucleobase;

M is an optionally protected internucleoside linkage;

20 q is from zero to about 50; and

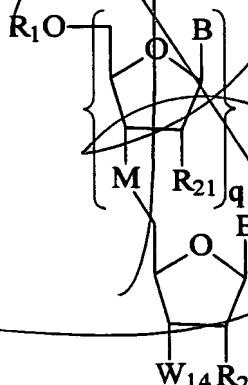
v is from zero to about 10.

22. A compound having formula XVIA, XVIB, XVIC or XVID:

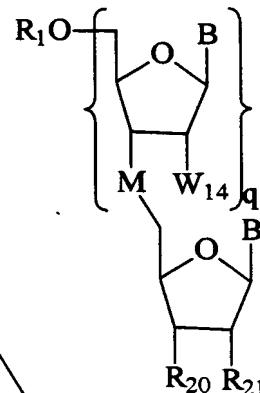


XVIA

XVIC



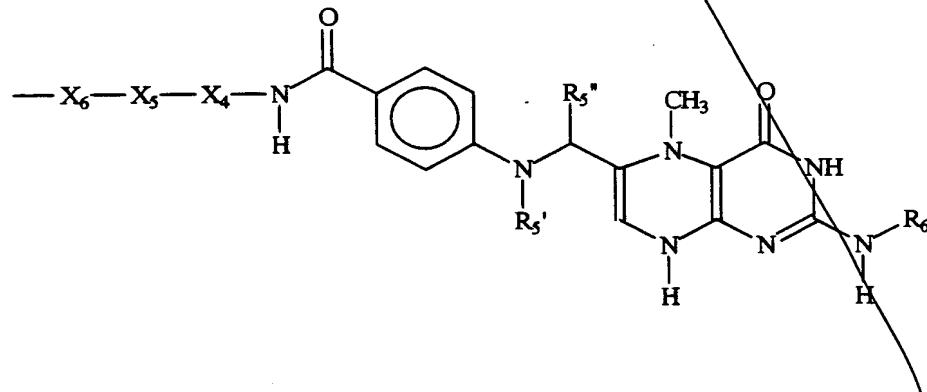
XVIB



XVID

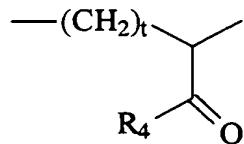
wherein:

W<sub>14</sub> has the formula:



wherein:

X<sub>4</sub> is -CH(X<sub>4'</sub>) or a group of formula:



X<sub>4'</sub> is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X<sub>5</sub> is -N(X<sub>6</sub>)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -C(S)NH-, -SC(S)NH-, -SC(O)NH-, -OC(S)NH-, -C(O)O-, -C(O)(CH<sub>2</sub>)<sub>n</sub>- or a bond;

n is an integer from 1 to 50;

each X<sub>6</sub> and X<sub>6'</sub> is, independently, a bond, hydrogen or a hydrocarbyl group selected from C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>6</sub>-C<sub>14</sub> aralkyl, C<sub>3</sub>-C<sub>14</sub> cycloalkyl, C<sub>5</sub>-C<sub>14</sub> fused cycloalkyl, C<sub>4</sub>-C<sub>14</sub> heterocycle, C<sub>4</sub>-C<sub>14</sub> heterocyclalkyl, C<sub>4</sub>-C<sub>14</sub> heteroaryl and C<sub>4</sub>-C<sub>14</sub> heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X<sub>6</sub> is not hydrogen and X<sub>6'</sub> is not a bond;

R<sub>1</sub> is hydrogen or a hydroxyl protecting group;

R<sub>4</sub> is a hydroxyl group or a protected hydroxyl group;

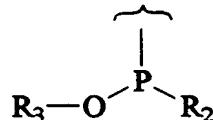
each R<sub>5</sub> and R<sub>40</sub> is, independently, hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>14</sub> aryl or an amino-protecting group

R<sub>50</sub> is hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>6</sub>-C<sub>14</sub> aralkyl, C<sub>3</sub>-C<sub>14</sub> cycloalkyl, formyl,

aminoalkyl or hydroxymethyl;

$R_6$  is hydrogen or an amino protecting group;

$R_{20}$  is hydrogen or a group of formula:



5  $R_2$  is  $-\text{N}(\text{R}_7)_2$ , or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

10  $R_7$  is straight or branched chain alkyl having from 1 to 10 carbons;

$R_3$  is a phosphorus protecting group;

15  $R_{21}$  is hydrogen, hydroxyl, fluoro or a group of formula  $Z-\text{R}_{22}-\text{(R}_{23}\text{)}_v$ ;

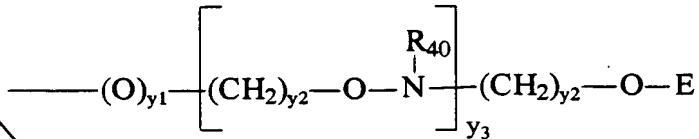
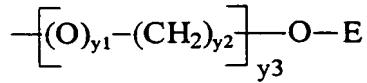
$Z$  is O, S, NH or  $\text{N}-\text{R}_{22}-\text{(R}_{23}\text{)}$ ;

20  $R_{22}$  is  $\text{C}_1-\text{C}_{20}$  alkyl,  $\text{C}_2-\text{C}_{20}$  alkenyl, or  $\text{C}_2-\text{C}_{20}$  alkynyl;

$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl,

25 amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or  $R_{21}$  has one of the formulas:



wherein:

y<sub>1</sub> is 0 or 1;

each y<sub>2</sub> is, independently, 0 to 10;

5 y<sub>3</sub> is 1 to 10;

E is N(R<sub>41</sub>)(R<sub>42</sub>) or N=C(R<sub>41</sub>)(R<sub>42</sub>);

each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub> alkyl, a nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken together form a nitrogen protecting group; or R<sub>41</sub> and R<sub>42</sub> taken together with 10 the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

B is a nucleobase;

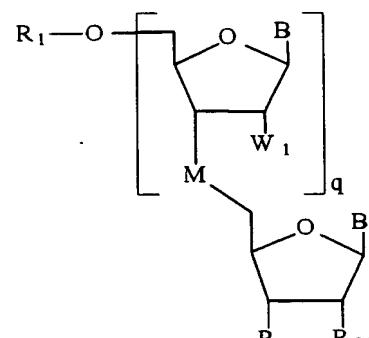
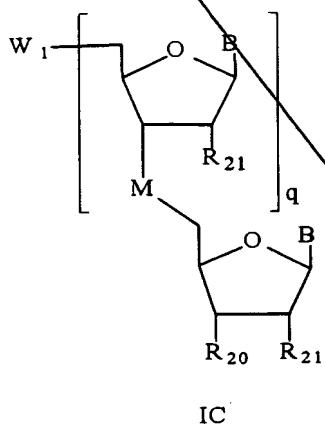
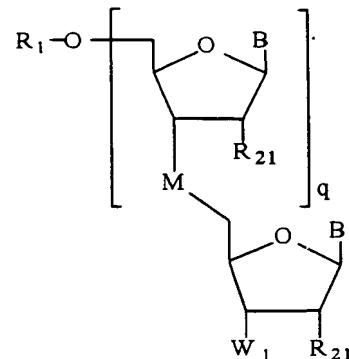
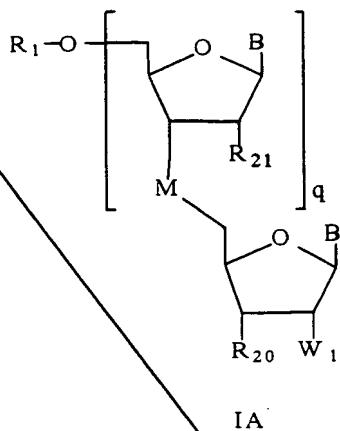
M is an optionally protected internucleoside linkage;

15 q is from zero to about 50; and

v is from zero to about 10.

23. A synthetic method comprising the steps of:

(a) providing a compound of formula IA, IB, IC or ID:



wherein:

W<sub>1</sub> is a linking group, O, NH, or S;

R<sub>1</sub> is H or a hydroxyl protecting group;

5 B is a nucleobase;

each R<sub>21</sub> is H, OH, F, or a group of formula Z-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>;

Z is O, S, NH, or N-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>

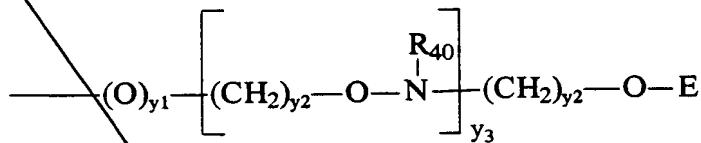
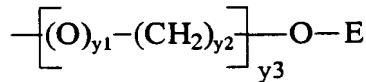
R<sub>22</sub> is C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>20</sub> alkenyl, or C<sub>2</sub>-C<sub>20</sub> alkynyl;

R<sub>23</sub> is hydrogen, amino, halogen, hydroxyl, thiol,

10 keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, 15 disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide,

polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

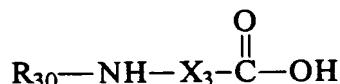
- 5 v is from 0 to about 10;  
or R<sub>21</sub> has one of the formulas:



wherein:

- 10 y<sub>1</sub> is 0 or 1;  
y<sub>2</sub> is 0 to 10;  
y<sub>3</sub> is 1 to 10;  
E is N(R<sub>41</sub>)(R<sub>42</sub>) or N=C(R<sub>41</sub>)(R<sub>42</sub>);  
each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub>  
alkyl, a nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken  
15 together form a nitrogen protecting group; or R<sub>41</sub> and R<sub>42</sub> taken  
together with the N or C atom to which they are attached form  
a ring structure that can include at least one heterotom  
selected from N and O;  
q is from 0 to about 50;
- 20 M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound  
of formula II:

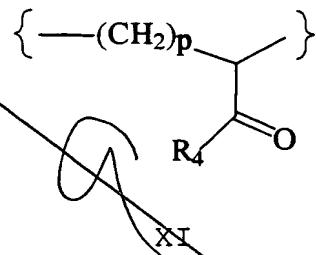


II

wherein:

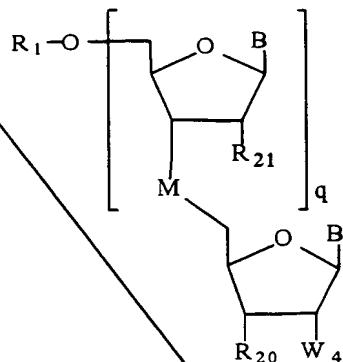
 $R_{30}$  is an amino protecting group; $X_3$  is  $-CH(Z_1)-$  or a group of Formula XI:

5

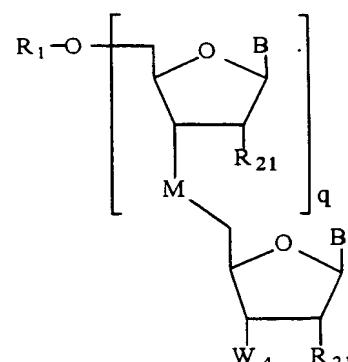


Z<sub>1</sub> is the sidechain of a naturally occurring amino acid,  
or a protected sidechain of a naturally occurring amino acid;  
p is 1 or 2;

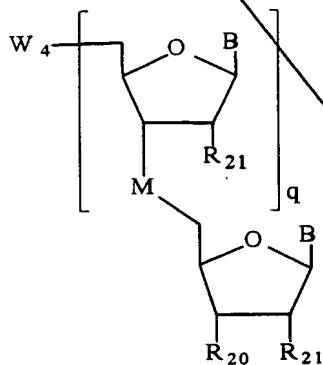
10 to form a compound of formula IVA, IVB, IVC, or IVD:



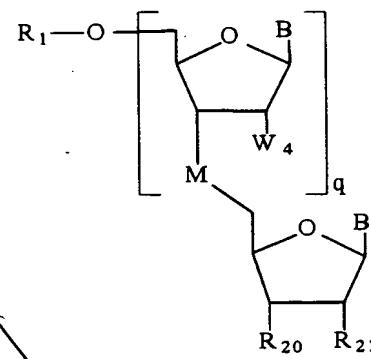
IVA



IVB



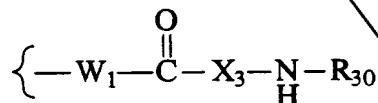
IVC



IVD

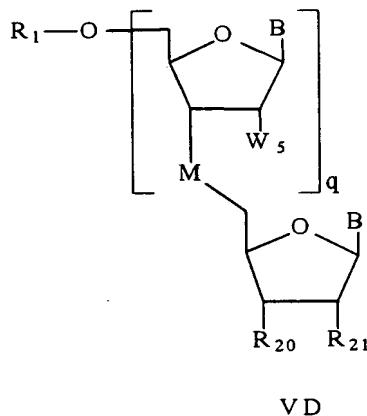
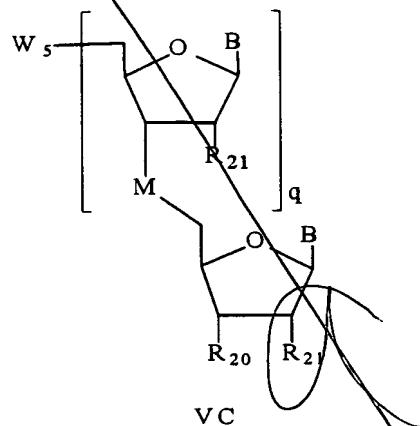
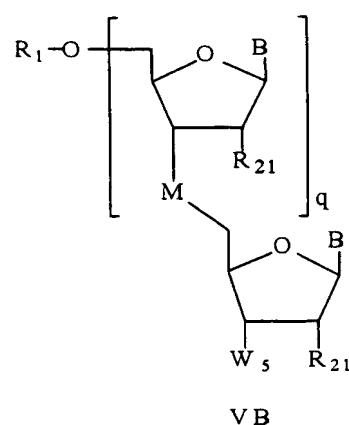
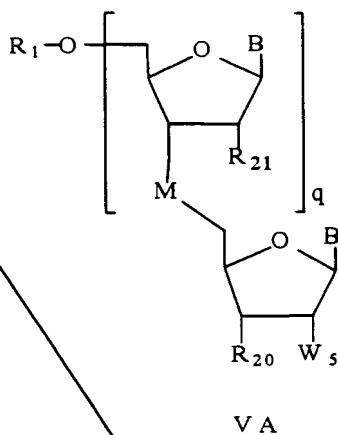
wherein:

$W_4$  has the formula:

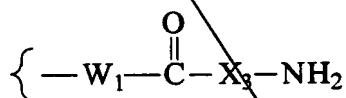


5 and

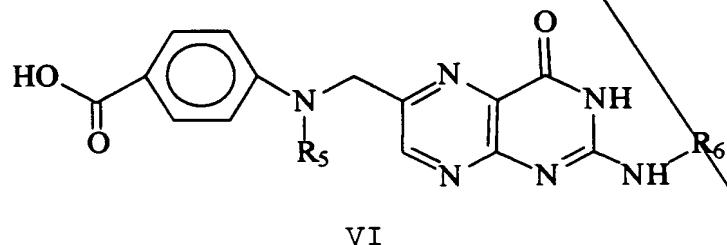
treating said compound of formula IVA, IVB, IVC or IVD  
with a deprotecting reagent to form a compound of formula VA,  
VB, VC or VD:



wherein  $W_5$  has the formula:



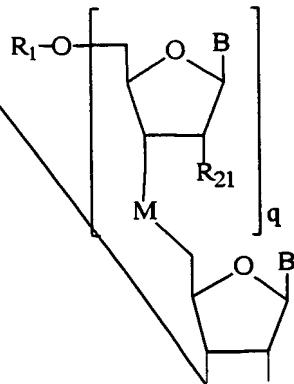
24. The method of claim 23 further comprising  
5 condensing said compound of formula V with a compound of  
formula VI:



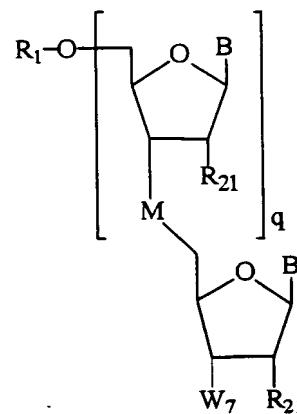
10 wherein:

$R_5$  is H or an amino protecting group;  
 $R_6$  is H or an amino protecting group;

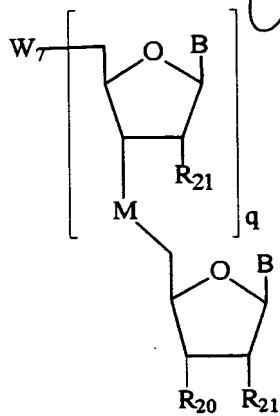
to form a compound of formula VIIA, VIIIB, VIIC, or VIID:



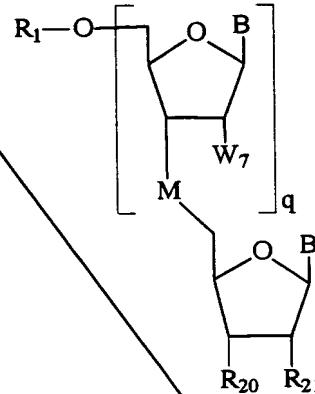
VIIA



VIIIB

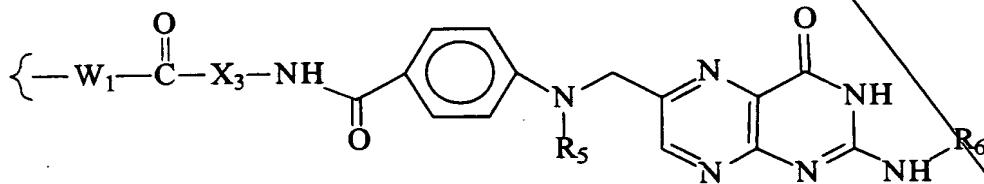


VIIC

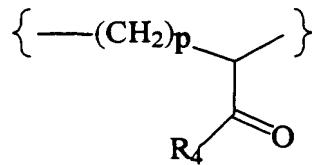


VIID

5 wherein  $W_7$  has the formula:



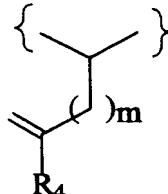
25. The method of claim 24 wherein  $X_3$  is a group of formula XI:



5 wherein:

p is 1 or 2;

R<sub>4</sub> is a hydroxyl group, or a protected hydroxy group; or  $X_3$  is a group of formula XII:



XII

10 wherein m is 1 or 2.

26. The method of claim 25 wherein q is 0.

27. The method of claim 25 wherein R<sub>30</sub> is fluorene-9-yl methoxycarbonyl.

15 28. The method of claim 25 wherein  $X_3$  is a group of formula XI.

29. The method of claim 25 wherein W<sub>1</sub> has the formula -O-(CH<sub>2</sub>)<sub>n</sub>-NH-, wherein n is from 1 to about 10.

30. The method of claim 29 wherein n is 6.

20 31. The method of claim 25 wherein  $X_3$  is a group of formula XII.

**B**

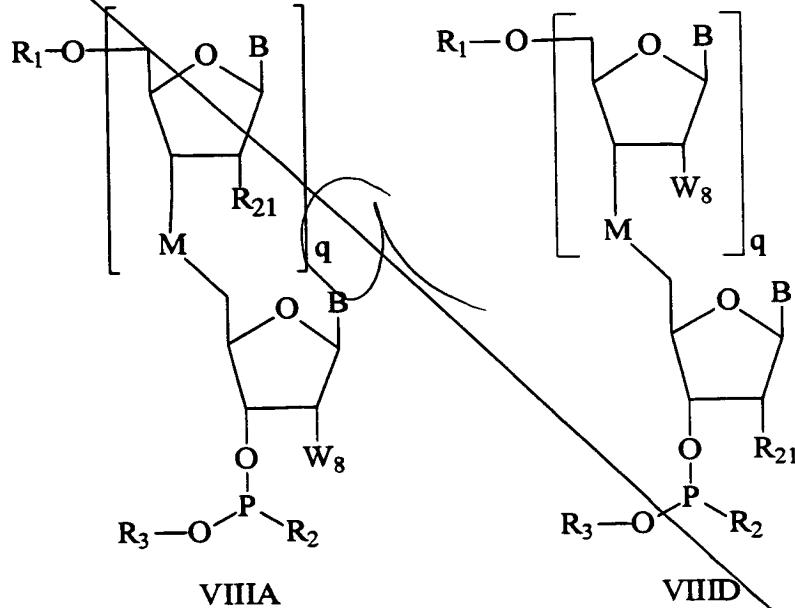
32. The method of claim 31 wherein  $W_1$  has the formula  $-O-(CH_2)_n-NH-$ , wherein n is from 1 to about 10.

33. The method of claim 32 wherein n is 6.

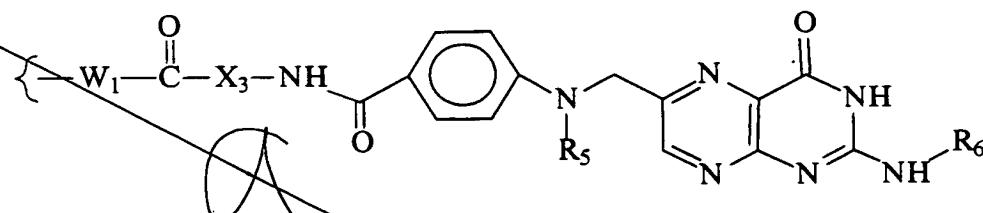
34. The method of claim 28 wherein  $R_1$  is dimethoxytrityl,  $W_1$  has the formula  $-O-(CH_2)_n-NH-$  where n is 6, p is 2,  $R_4$  is t-butoxy,  $R_5$  is trifluoroacetyl,  $R_6$  is  $-C(=O)-CH(CH_3)_2$ , and  $R_{30}$  is FMOC.

*Sub  
B4* 35. The method of claim 31 wherein  $R_1$  is dimethoxytrityl, A has the formula  $-O-(CH_2)_n-NH-$  where n is 6, m is 2,  $R_4$  is t-butoxy,  $R_5$  is trifluoroacetyl,  $R_6$  is  $-C(=O)-CH(CH_3)_2$ , and  $R_{30}$  is FMOC.

36. The method of claim 24 further comprising contacting said compound of formula VIIA or VIID with a phosphitylating reagent to form a compound of formula VIIIA or VIIID:



wherein  $W_7$  has the formula:



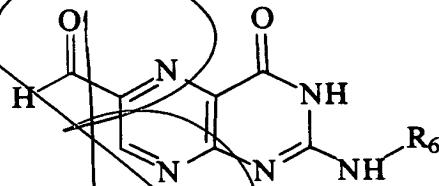
37. The method of claim 36 wherein  $\text{X}_3$  has the formula XI.

5 38. The method of claim 36 wherein  $\text{X}_3$  has the formula XII.

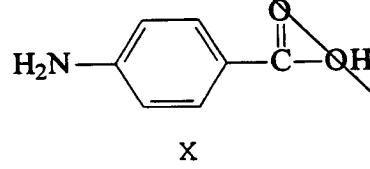
39. The method of claim 37 wherein  $\text{R}_1$  is dimethoxytrityl,  $\text{W}_1$  has the formula  $-\text{O}-\text{(CH}_2\text{)}_n-\text{NH}-$  where  $n$  is 6,  $\text{p}$  is 2,  $\text{R}_4$  is t-butoxy,  $\text{R}_5$  is trifluoroacetyl,  $\text{R}_6$  is  $-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)_2$ , and  $\text{R}_{30}$  is FMOC.

*Sub 35*  
40. The method of claim 38 wherein  $\text{R}_1$  is dimethoxytrityl,  $\text{W}_1$  has the formula  $-\text{O}-\text{(CH}_2\text{)}_n-\text{NH}-$  where  $n$  is 6,  $\text{m}$  is 2,  $\text{R}_4$  is t-butoxy,  $\text{R}_5$  is trifluoroacetyl,  $\text{R}_6$  is  $-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)_2$ , and  $\text{R}_{30}$  is FMOC.

15 41. The method of claim 25 wherein said compound of formula VI is prepared by the steps of reacting a compound of formula IX:

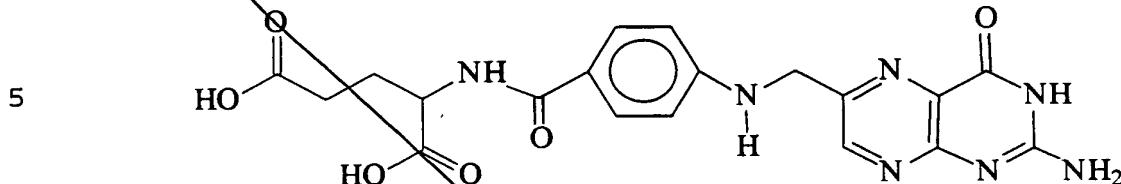


20 with a compound of formula X:

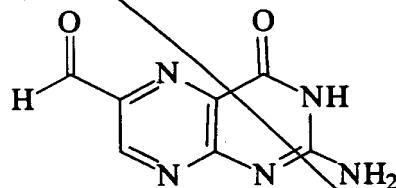


and treating the product of said reaction with a protecting group reagent to form said compound of formula VI.

*B Step C1* 42. The method of claim 26 wherein said compound IX is prepared by reacting folic acid:



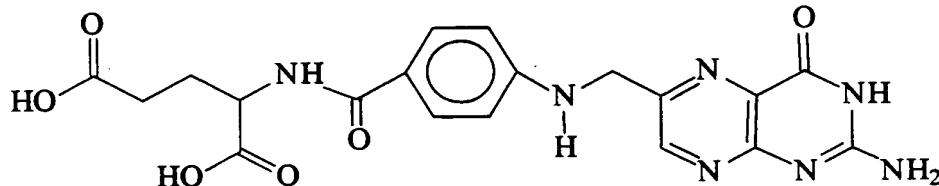
with a reagent effective to form pterin aldehyde:



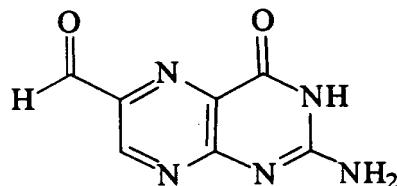
and

protecting the amino group of said pterin aldehyde.

10 43. A method for the preparation of a folic acid derivative comprising the steps of reacting folic acid:

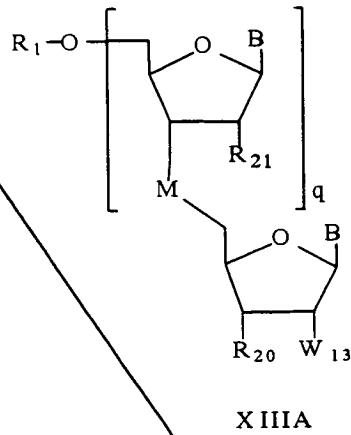


with a reagent effective to form pterin aldehyde:

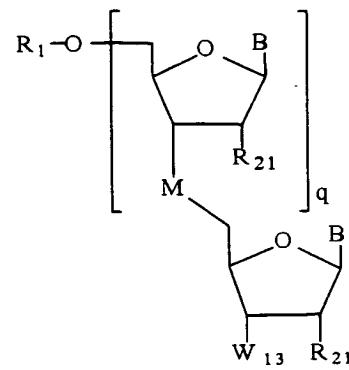


15 44. The method of claim 43 further comprising protecting the amino group of said pterin aldehyde.

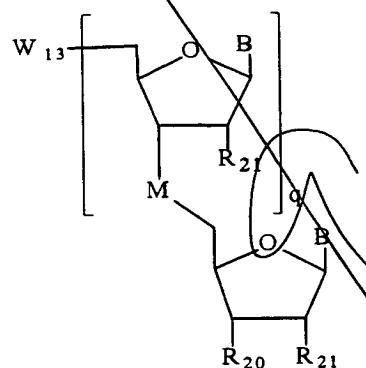
45. A compound having the formula XIIIA, XIIIB, XIIIC or XIIID:



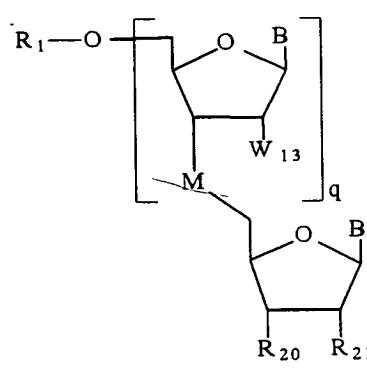
XIIIA



XIIIB



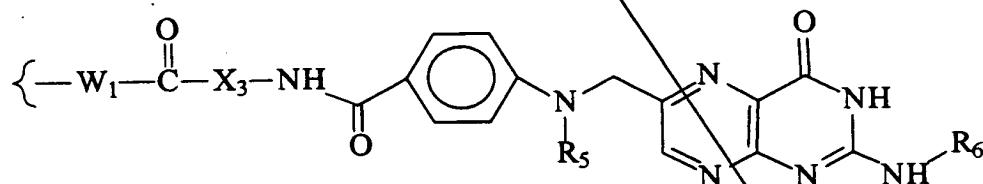
XIIIC



XIIID

wherein:

5       $W_{13}$  has the formula:



10       $R_1$  is H or a hydroxyl protecting group;

$B$  is a nucleobase;

each  $R_{21}$  is H, OH, F, or a group of formula  $Z-\text{R}_{22}-\text{(R}_{23}\text{)}_v$ ;

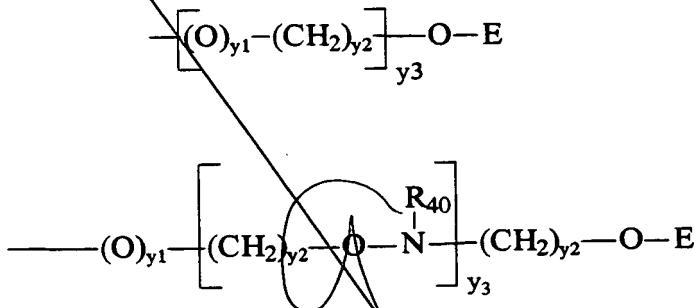
$Z$  is O, S, NH or  $N-\text{R}_{22}-\text{(R}_{23}\text{)}_v$ ;

$\text{R}_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

$\text{R}_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol,

keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino,  
5 hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group  
10 that enhances the pharmacokinetic properties of oligonucleotides;

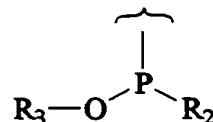
or  $R_{21}$  has one of the formulas:



wherein:

- 15            y1 is 0 or 1;  
              y2 is 0 to 10;  
              y3 is 1 to 10;  
              E is N(R<sub>41</sub>) (R<sub>42</sub>) or N=C(R<sub>41</sub>) (R<sub>42</sub>);  
              each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub>  
20 alkyl, a nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken  
together form a nitrogen protecting group; or R<sub>41</sub> and R<sub>42</sub> taken  
together with the N or C atom to which they are attached form  
a ring structure that can include at least one heteroatom  
selected from N and O;  
25            v is from 0 to about 10;  
              q is from 0 to about 50;  
              M is an optionally protected internucleoside linkage;  
              W<sub>1</sub> is a linking group, O, NH or S;

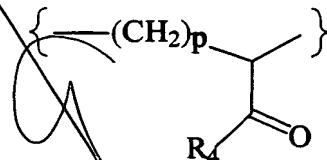
R<sub>20</sub> is H or a group of Formula:



R<sub>2</sub> is -N(R<sub>7</sub>)<sub>2</sub>, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R<sub>7</sub> is straight or branched chain alkyl having from 1 to 10 carbons;

- R<sub>3</sub> is a phosphorus protecting group;  
10 n is from 1 to about 10;  
R<sub>5</sub> is H or an amino protecting group;  
R<sub>6</sub> is H or an amino protecting group;  
X<sub>3</sub> is -CH(Z<sub>1</sub>)- or a group of Formula XI:



15 Z<sub>1</sub> is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

p is 1 or 2; and  
20 R<sub>4</sub> is a hydroxyl group, or a protected hydroxy group.

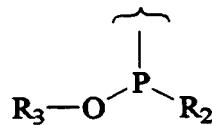
46. The compound of claim 45 wherein W<sub>1</sub> is -O-(CH<sub>2</sub>)<sub>n</sub>-NH- where n is from 1 to about 10.

47. The compound of claim 45 wherein n is 6.

48. The compound of claim 45 wherein R<sub>1</sub> is

dimethoxytrityl, R<sub>5</sub> is trifluoroacetyl, and R<sub>6</sub> is  
-C(=O)-CH(CH<sub>3</sub>)<sub>2</sub>, and R<sub>4</sub> is t-butoxy.

49. The compound of claim 45 wherein q is 0.
50. The compound of claim 45 wherein R<sub>20</sub> is a group of  
5 formula:



wherein R<sub>3</sub> is β-cyanoethyl, and R<sub>2</sub> is diisopropylamino.

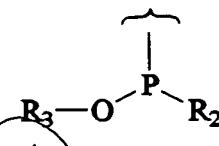
51. The compound of claim 50 wherein W<sub>1</sub> is  
-O-(CH<sub>2</sub>)<sub>6</sub>-NH-, R<sub>1</sub> is dimethoxytrityl, R<sub>5</sub> is  
10 trifluoroacetyl, R<sub>6</sub> is -C(=O)-CH(CH<sub>3</sub>)<sub>2</sub>, and R<sub>4</sub> is t-butoxy.

52. The compound of claim 50 wherein q is 0.
53. The compound of claim 45 wherein X<sub>3</sub> has the formula  
XI.

54. The compound of claim 53 wherein p is 2.
- 15 55. The compound of claim 54 wherein W<sub>1</sub> is  
-O-(CH<sub>2</sub>)<sub>6</sub>-NH-.
56. The compound of claim 55 wherein R<sub>4</sub> is t-butoxy.
57. The compound of claim 56 wherein R<sub>1</sub> is  
dimethoxytrityl, R<sub>5</sub> is trifluoroacetyl, and R<sub>6</sub> is  
20 -C(=O)-CH(CH<sub>3</sub>)<sub>2</sub>.

58. The compound of claim 57 wherein q is 0.

59. The compound of claim 58 wherein  $R_{20}$  is a group of formula:

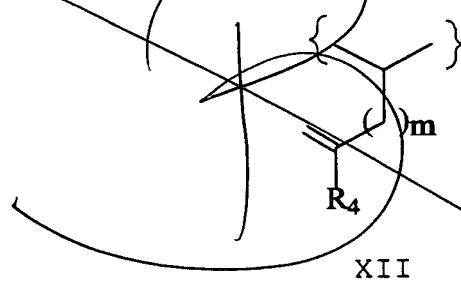


wherein R<sub>3</sub> is  $\beta$ -cyanoethyl, and R<sub>2</sub> is diisopropylamino.

5 60. The compound of claim 57 wherein R<sub>20</sub> is H.

61. The compound of claim 60 wherein q is 0.

62. The compound of claim 45 wherein X<sub>3</sub> has the formula XII:



10

wherein m is 1 or 2.

B

63. The compound of claim 62 wherein m is 2. <sup>107</sup>

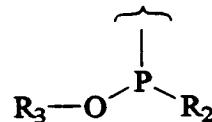
64. The compound of claim 63 wherein W<sub>1</sub> is  
-O-(CH<sub>2</sub>)<sub>6</sub>-NH-.

15 *Sub B* 65. The compound of claim 54 wherein R<sub>4</sub> is t-butoxy.

66. The compound of claim 65 wherein R<sub>1</sub> is dimethoxytrityl, R<sub>5</sub> is trifluoroacetyl, and R<sub>6</sub> is -C(=O)-CH(CH<sub>3</sub>)<sub>2</sub>.

67. The compound of claim 66 wherein q is 0.

68. The compound of claim 67 wherein  $R_{20}$  is a group of formula:

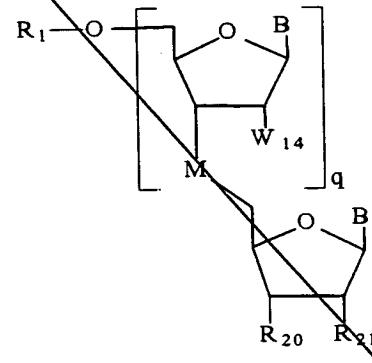
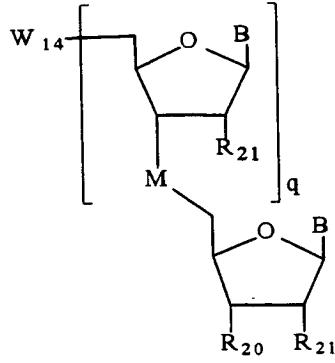
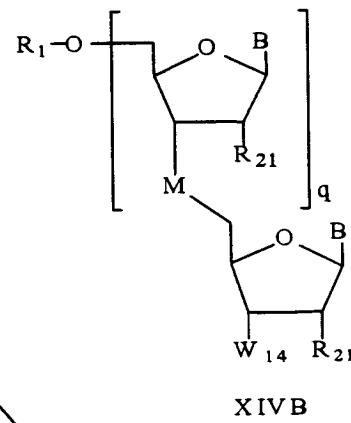
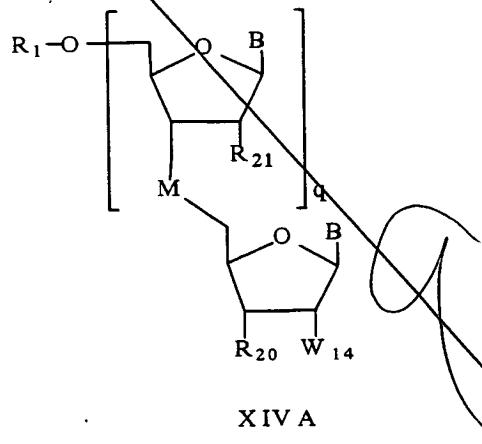


where  $R_3$  is  $\beta$ -cyanoethyl, and  $R_2$  is diisopropylamino.

5 69. The compound of claim 45 wherein  $R_{20}$  is H.

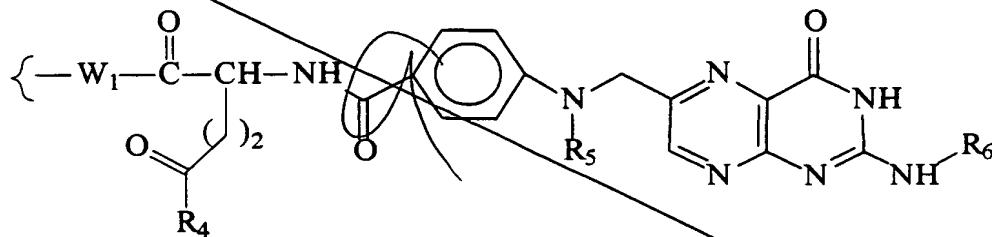
70. The compound of claim 69 wherein  $q$  is 0.

71. A composition comprising a compound of claim 54, said composition being substantially free of a compound of formula XIVA, XIVB, XIVC, or XIVD:

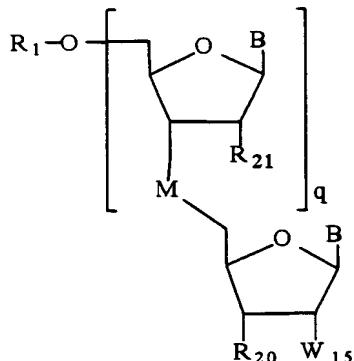


wherein:

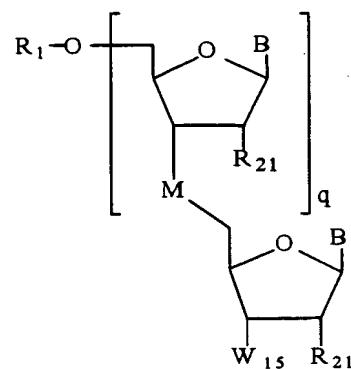
$W_{14}$  has the formula:



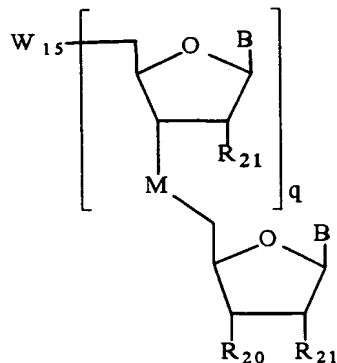
72. A composition comprising a compound of claim 63,  
5 said composition being substantially free of a compound of  
formula XVA, XVB, XVC or XVD:



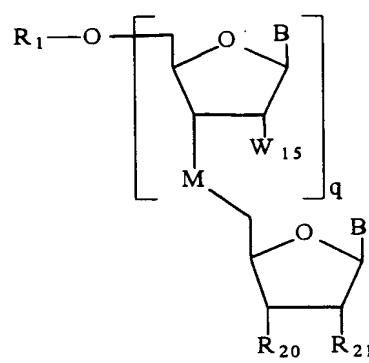
XVA



XVB



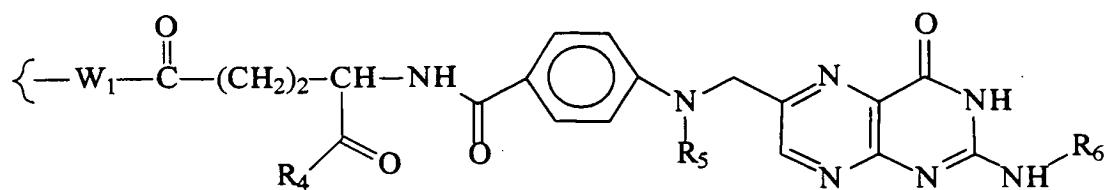
XVC



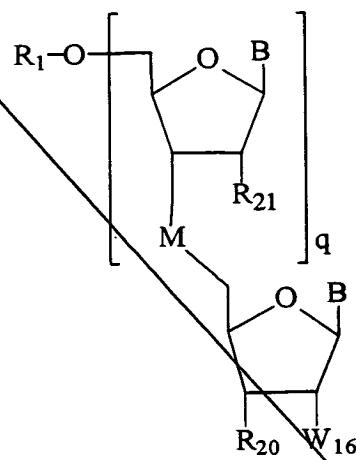
XVD

wherein  $W_{15}$  has the formula:

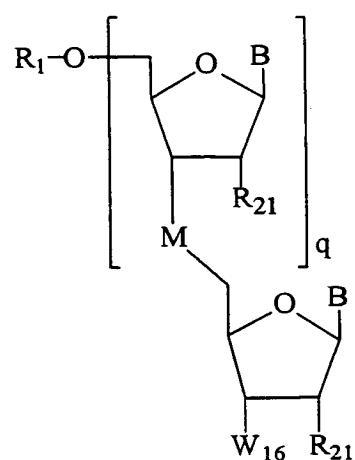
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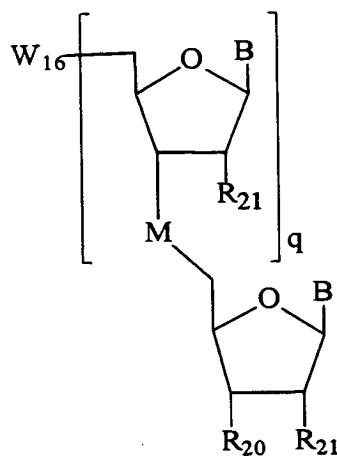
73. A compound having the formula XVIA, XVIB, XVIC or XVID:



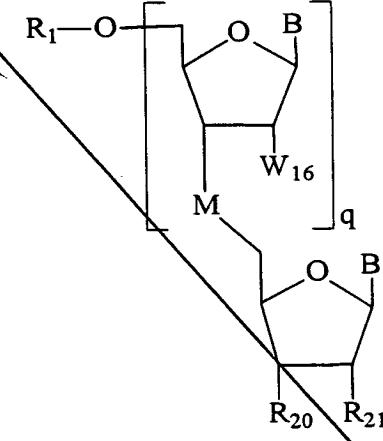
XVIA



XVIB



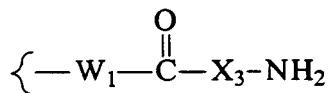
XVIC



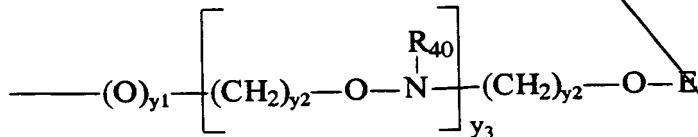
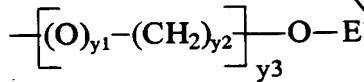
XVID

5 wherein:

$W_{16}$  has the formula:



R<sub>1</sub> is H or a hydroxyl protecting group;  
 B is a nucleobase;  
 each R<sub>21</sub> is H, OH, F, or a group of formula Z-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>;  
 5 Z is O, S, NH or N-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>;  
 R<sub>22</sub> is C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>20</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>1</sub>-C<sub>20</sub> alkoxy, C<sub>2</sub>-C<sub>20</sub> alkenyloxy, or C<sub>2</sub>-C<sub>20</sub> alkynyloxy;  
 R<sub>23</sub> is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, 10 trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, inter- 15 calator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;  
 20 or R<sub>21</sub> has one of the formulas:



wherein:

y<sub>1</sub> is 0 or 1;  
 y<sub>2</sub> is 0 to 10;  
 25 y<sub>3</sub> is 1 to 10;

E is  $N(R_{41})(R_{42})$  or  $N=C(R_{41})(R_{42})$ ;  
 each  $R_{41}$  and each  $R_{42}$  is independently H,  $C_1-C_{10}$   
 alkyl, a nitrogen protecting group, or  $R_{41}$  and  $R_{42}$  taken  
 together form a nitrogen protecting group; or  $R_{41}$  and  $R_{42}$  taken  
 5 together with the N or C atom to which they are attached form  
 a ring structure that can include at least one heterotom  
 selected from N and O;

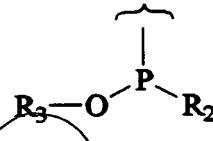
v is from 0 to about 10;

q is from 0 to about 50;

10 M is an optionally protected internucleoside linkage;

$W_1$  is a linking group;

$R_{20}$  is H or a group of Formula:



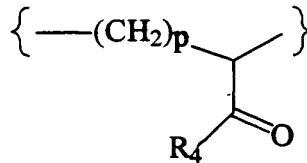
15  $R_2$  is  $-N(R_7)_2$ , or a heterocycloalkyl or  
 heterocycloalkenyl ring containing from 4 to 7 atoms, and  
 having up to 3 heteroatoms selected from nitrogen, sulfur,  
 and oxygen;

$R_7$  is straight or branched chain alkyl having from 1 to  
 10 carbons;

20  $R_3$  is a phosphorus protecting group;

n is from 1 to about 10;

$X_3$  is  $-CH(Z_1)-$  or a group of Formula XI:



XI

25  $Z_1$  is the sidechain of a naturally occurring amino acid,  
 or a protected sidechain of a naturally occurring amino acid;  
 and

p is 1 or 2.

74. The compound of claim 73 wherein  $X_3$  has the formula  
XI.

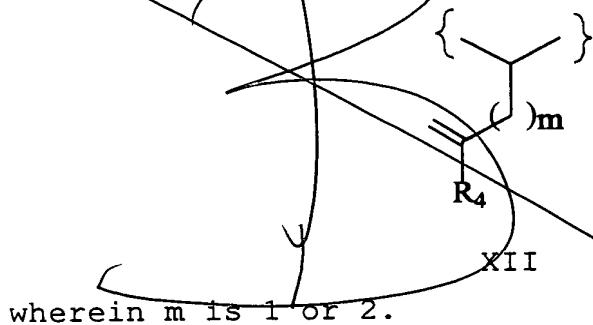
75. The compound of claim 74 wherein p is 2.

5 76. The compound of claim 75 wherein  $W_1$  is  $-O-(CH_2)_n-NH-$   
wherein n is from 1 to about 10.

77. The compound of claim 76 wherein n is 6.

78. The compound of claim 73 wherein  $X_3$  has the formula  
XII:

10

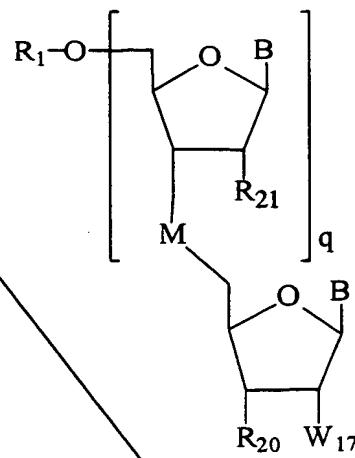


79. The compound of claim 78 wherein m is 2.

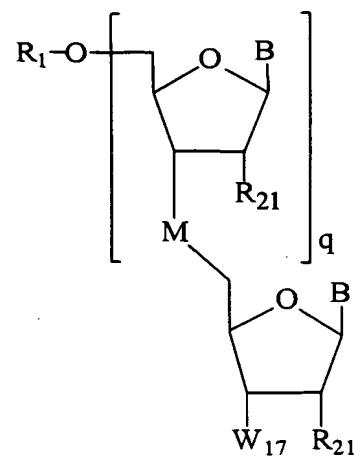
80. The compound of claim 79 wherein  $W_1$  is  $-O-(CH_2)_n-NH-$   
15 wherein n is from 1 to about 10.

81. The compound of claim 80 wherein n is 6.

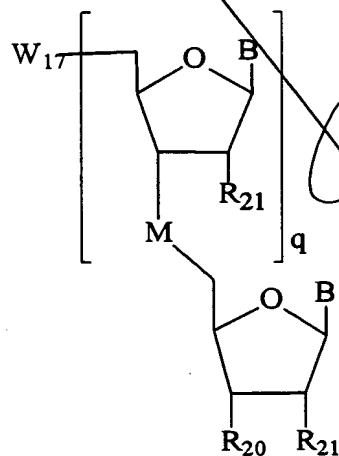
82. A compound having the formula XVIIA, XVIIB, XVIIC  
or XVIID:



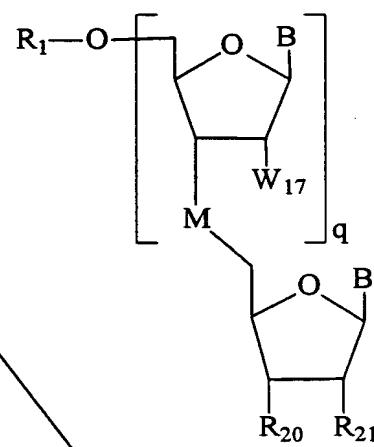
XVIIA



XVIIIB



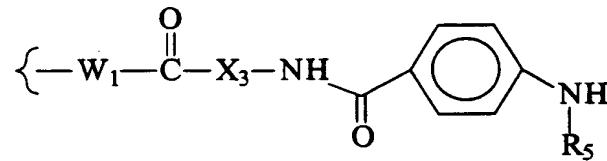
XVIIC



XVIID

wherein:

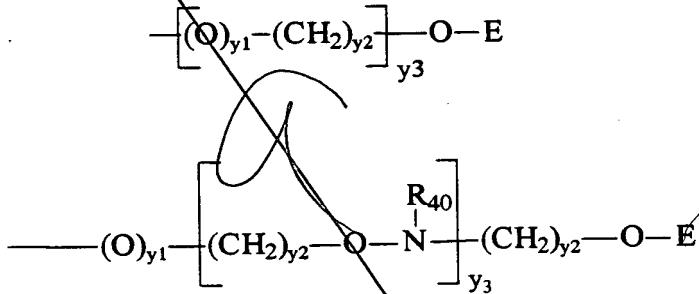
$W_{17}$  has the formula:



- 5       $R_1$  is H or a hydroxyl protecting group;  
 B is a nucleobase;  
 each  $R_{21}$  is H, OH, F, or a group of formula  $Z-R_{22}-(R_{23})_v$ ;

Z is O, S, NH or N-R<sub>22</sub>- (R<sub>23</sub>)<sub>v</sub>;  
 R<sub>22</sub> is C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>20</sub> alkenyl, or C<sub>2</sub>-C<sub>20</sub> alkynyl;  
 R<sub>23</sub> is hydrogen, amino, halogen, hydroxyl, thiol, keto,  
 carboxyl, nitro, nitroso, nitrile, trifluoromethyl,  
 5 trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-  
 aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl,  
 amino, N-phthalimido, imidazole, azido, hydrazino,  
 hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide,  
 disulfide, silyl, aryl, heterocycle, carbocycle, inter-  
 10 calator, reporter molecule, conjugate, polyamine, polyamide,  
 polyalkylene glycol, polyether, a group that enhances the  
 pharmacodynamic properties of oligonucleotides, or a group  
 that enhances the pharmacokinetic properties of oligonucleo-  
 tides;

15 or R<sub>21</sub> has one of the formulas:



wherein:

20 y<sub>1</sub> is 0 or 1;  
 y<sub>2</sub> is 0 to 10;  
 y<sub>3</sub> is 1 to 10;  
 E is N(R<sub>41</sub>) (R<sub>42</sub>) or N=C(R<sub>41</sub>) (R<sub>42</sub>);  
 each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub>  
 alkyl, a nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken  
 together form a nitrogen protecting group; or R<sub>41</sub> and R<sub>42</sub> taken  
 25 together with the N or C atom to which they are attached form  
 a ring structure that can include at least one heterotom  
 selected from N and O;

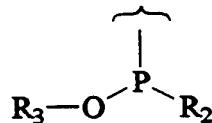
v is from 0 to about 10;

q is from 0 to about 50;

M is an optionally protected internucleoside linkage;

W<sub>1</sub> is a linking group, O, NH or S;

R<sub>20</sub> is H or a group of formula:



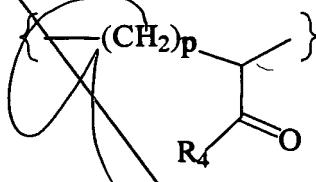
5 R<sub>2</sub> is -N(R<sub>7</sub>)<sub>2</sub>, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

10 R<sub>7</sub> is straight or branched chain alkyl having from 1 to 10 carbons;

R<sub>3</sub> is a phosphorus protecting group;

n is from 1 to about 10;

X<sub>3</sub> is -CH(Z<sub>1</sub>)- or a group of formula XI:



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Z<sub>1</sub> is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

p is 1 or 2; and

R<sub>5</sub> is H or an amino protecting group.

20 83. The compound of claim 82 wherein X<sub>3</sub> has the formula XI.

84. The compound of claim 83 wherein p is 2.

85. The compound of claim 84 wherein W<sub>1</sub> is -O-(CH<sub>2</sub>)<sub>n</sub>-NH- wherein n is from 1 to about 10.

86. The compound of claim 85 wherein n is 6.

87. The compound of claim 82 wherein  $X_3$  has the formula  
XII:

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XIII

wherein m is 1 or 2.

88. The compound of claim 87 wherein m is 2.

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89. The compound of claim 88 wherein  $W_1$  is  $-O-(CH_2)_n-NH-$   
wherein n is from 1 to about 10.

10 90. The compound of claim 89 wherein n is 6.

91. A folate conjugate comprising a folate moiety  
covalently linked to an amino acid, said amino acid further  
connected to a hydrocarbyl group, said hydrocarbyl group  
bearing at least two hydroxyl groups.

15 92. An oligonucleotide-folate conjugate comprising a  
folate moiety covalently linked to an amino acid, said amino  
acid being connected to a hydrocarbyl group, said hydrocarbyl  
group further connected to an oligonucleotide, said  
hydrocarbyl group bearing at least two hydroxyl groups.

B 20 93. The compound of claim 92 wherein said  $R_4$  is a  
hydroxyl group protected with  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl or  
 $C_2-C_{20}$  alkynyl.

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94. The compound of claim 13 wherein said  $R_4$  is a

hydroxyl group protected with C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>20</sub> alkynyl.

95. The compound of claim 16 wherein said R<sub>4</sub> is a hydroxyl group protected with C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or 5 C<sub>2</sub>-C<sub>20</sub> alkynyl.

96. The method of claim 19 wherein said R<sub>4</sub> is a hydroxyl group protected with C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>20</sub> alkynyl;  
further comprising the step of deprotecting said R<sub>4</sub> with a 10 deprotecting reagent.

97. The method of claim 96 wherein said deprotecting reagent is an aqueous amine.

98. The method of claim 97 wherein said amine is piperidine, pyrrolidine, piperazine or morpholine.

15 99. The method of claim 96 wherein said deprotecting reagent comprises an aqueous amine and a mercapto compound.

100. The method of claim 99 wherein the concentration of said mercapto compound is 2-10%.

add  
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